Dec-30-2005

Attorney Docket No. 42896-261843

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Emanuele et al.

Serial No.: **09/919,504**

Filed: **July 31, 2001**

For: **THERAPEUTIC DELIVERY COMPOSITIONS AND METHODS OF USE THEREOF**

Group Art Unit: **1635**

Examiner: **Schnizer, Richard A**

APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellants submit this paper together with Form PTO 2038 in the amount of $500.00 pursuant to 37 C.F.R.§41.20(b)(2). Appellants also submit a petition for a four-month extension of time, now set to expire December 27, 2005, and Form PTO 2038 for the appropriate fee for the extension of time. The Commissioner is authorized to debit Deposit Account No. 11-0855 for any additional fee.

I. Real Party in Interest

The real party in interest is CytRx Corporation, of Los Angeles, California, the owner of the above-referenced application.

01/05/2006 HTECKLU1 00000005 09919504
01 FC:1402 500.00 OP

II. Related Appeals and Interferences

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on December 27, 2005.

Z. Doddridge

Zara A. Doddridge – Limited Reg. No. L0030

01/03/2006 HTECKLU1 00000040 09919504
02 FC:1401 500.00 OP

Appellants are unaware of any appeal or interference that will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. Status of Claims

On May 27, 2005, appellants appealed from the final rejection of Claims 1- 42.

Claims 1- 42 are pending and were rejected by the Examiner in the Office Action mailed December 1, 2004 and the Advisory Action mailed February 24, 2005.

Claims 1- 42 are on appeal.

IV. Status of Amendments

No amendment has been submitted subsequent to the Final rejection.

V. Summary of Claimed Subject Matter

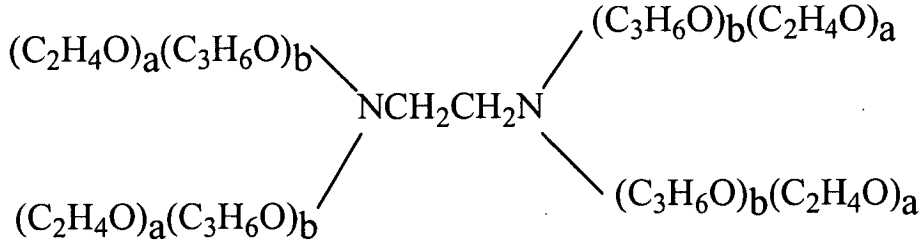
A. Concise Explanation

Appellants claim compositions comprising one or more nucleic acid sequences selected from a particular group and an octablock copolymer having a particular chemical formula (Claims 1-18, 39 and 41). Appellants also claim methods of delivering a molecule to an animal comprising administering to the animal a composition comprising one or more nucleic acid sequences from a particular group and an octablock copolymer having a particular formula (Claims 19-38, 40, and 42). The compositions facilitate transportation and, therefore, delivery of a genetic-based therapeutic to the interior of cells.

The octablock copolymers of Claims 1-42 are described in the specification, for example, on page 23, line 11 to page 28, line 11 and in the Examples on page 31, line 4 to page 37, line 12. The nucleic acid sequences of Claims 1-42 are described in the specification, for example, on page 29, line 32 to page 30, line 9 and in the Examples on page 31, line 4 to page 37, line 12.

More specifically, Claim 1 recites a composition comprising one or more nucleic acid sequences selected from the group consisting of oligonucleotides, antisense oligonucleotides, triplex DNA compounds, ribozymes, and mixtures thereof; and

an octablock copolymer, wherein the octablock copolymer has the following formula:



wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is between about 5000 and about 7000 Daltons;

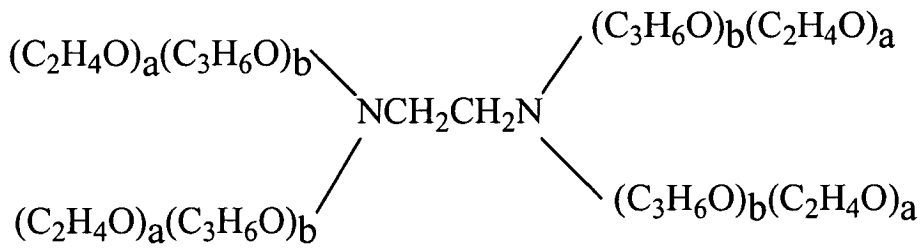
a is a number such that the portion represented by polyoxyethylene constitutes between about 10% and about 40% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes between about 60% and about 90% of the octablock copolymer by weight. See the specification at page 7, line 16-page 8, line 14; page 12, line 34-page 13, line 1; and original Claim 1.

Claim 8 recites a composition comprising,

one or more nucleic acid sequences which encode a gene product; and

an octablock copolymer, wherein the octablock copolymer has the following formula:



wherein:

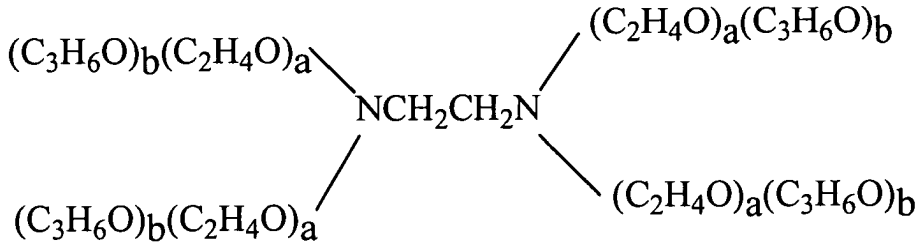
the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is between about 5000 and about 7000 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes between about 10% and about 40% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes between about 60% and about 90% of the octablock copolymer by weight. See the specification at page 7, line 16-page 8, line 14; page 9, lines 9-15; and original Claim 1.

Claim 9 recites a composition comprising,

one or more nucleic acid sequences selected from the group consisting of oligonucleotides, antisense oligonucleotides, triplex DNA compounds, ribozymes, and mixtures thereof; and an octablock copolymer, wherein the octablock copolymer has the following formula:



wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is between about 5000 and about 7000 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes between about 10% and about 40% of the octablock copolymer by weight; and

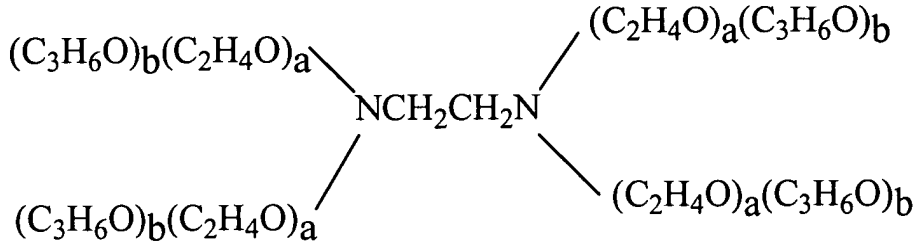
b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes between about 60% and about

90% of the octablock copolymer by weight. See the specification at page 8, line 15-page 9, line 9; page 12, line 34-page 13, line 1; and original Claim 9.

Claim 16 recites a composition comprising,

one or more nucleic acid sequences which encode a gene product; and

an octablock copolymer, wherein the octablock copolymer has the following formula:



wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is between about 5000 and about 7000 Daltons;

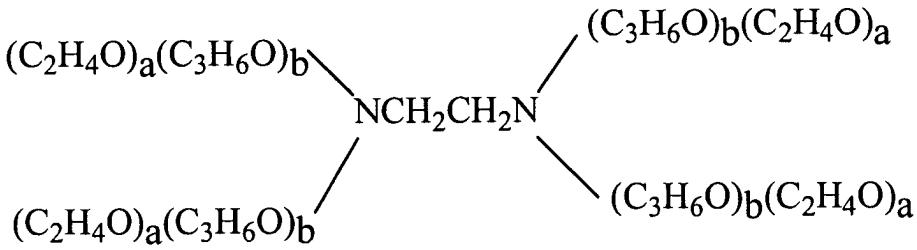
a is a number such that the portion represented by polyoxyethylene constitutes between about 10% and about 40% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes between about 60% and about 90% of the octablock copolymer by weight. See the specification at page 8, line 15-page 9, line 9; page 9, lines 10-15; and original Claim 9.

Claim 17 recites a composition comprising,

one or more nucleic acid sequences selected from the group consisting of oligonucleotides, antisense oligonucleotides, triplex DNA compounds, ribozymes, and mixtures thereof; and

an octablock copolymer, wherein the octablock copolymer has the following formula:



wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is between about 5000 and about 7000 Daltons;

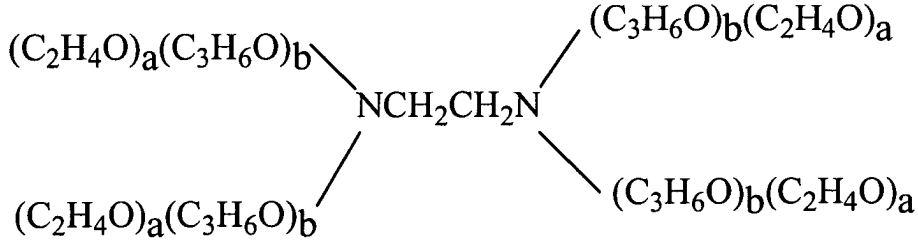
a is a number such that the portion represented by polyoxyethylene constitutes between about 5% and about 20% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes between about 80% and about 95% of the octablock copolymer by weight. See the specification at page 7, line 16-page 8, line 14; page 12, line 34-page 13, line 1; page 25, lines 15-22; original Claim 17 and Table II.

Claim 19 recites a method of delivering a molecule to an animal comprising,

administering to the animal a composition comprising one or more nucleic acid sequences selected from the group consisting of oligonucleotides, antisense oligonucleotides, triplex DNA compounds, ribozymes, and mixtures thereof; and

an octablock copolymer, wherein the octablock copolymer has the following formula:



wherein:

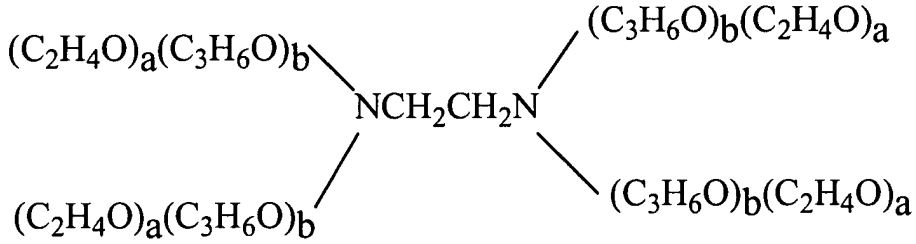
the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is between about 5000 and about 7000 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes between about 10% and about 40% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes between about 60% and about 90% of the octablock copolymer by weight. See the specification at page 7, line 16-page 8, line 14; and page 12, line 34-page 13, line 1 and original Claim 19.

Claim 26 recites a method of delivering a molecule to an animal comprising,

administering to the animal a composition comprising one or more nucleic acid sequences which encode a gene product, and an octablock copolymer, wherein the octablock copolymer has the following formula:



wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is between about 5000 and about 7000 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes between about 10% and about 40% of the octablock copolymer by weight; and

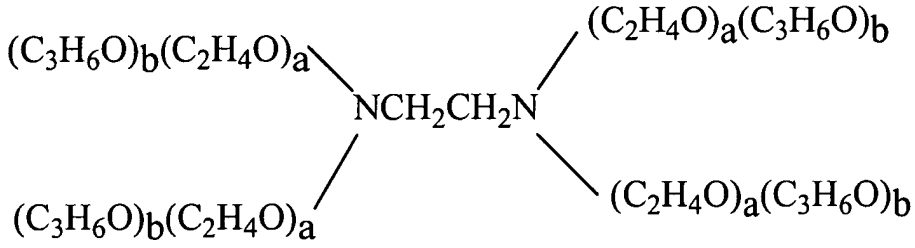
b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes between about 60% and about

90% of the octablock copolymer by weight. See the specification at page 7, line 16-page 8, line 14; page 9, lines 9-15; original Claim 19 and page 16, lines 3-14.

Claim 27 recites a method of delivering a molecule to an animal comprising,

administering to the animal a composition comprising one or more nucleic acid sequences selected from the group consisting of oligonucleotides, antisense oligonucleotides, triplex DNA compounds, ribozymes, and mixtures thereof; and

an octablock copolymer, wherein the octablock copolymer has the following formula:



wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is between about 5000 and about 7000 Daltons;

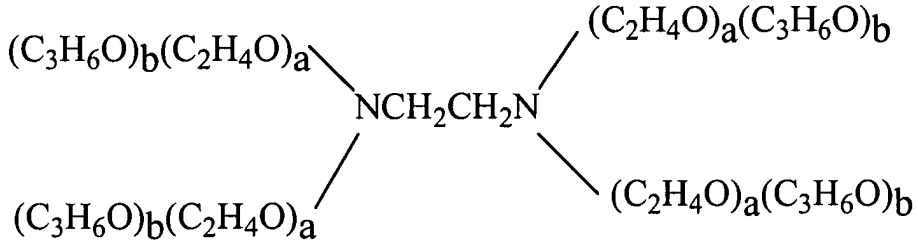
a is a number such that the portion represented by polyoxyethylene constitutes between about 10% and about 40% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes between about 60% and about 90% of the octablock copolymer by weight. See the specification at page 8, line 15-page 9, line 9; page 12, line 34-page 13, line1; and original Claim 27.

Claim 33 recites a method of delivering a molecule to an animal comprising,

administering to the animal one or more nucleic acids sequences selected from the group consisting of oligonucleotides, antisense oligonucleotides, triplex DNA

compounds, ribozymes, and mixtures thereof; and an octablock copolymer, wherein the octablock copolymer has the following formula:



wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is between about 5000 and about 7000 Daltons;

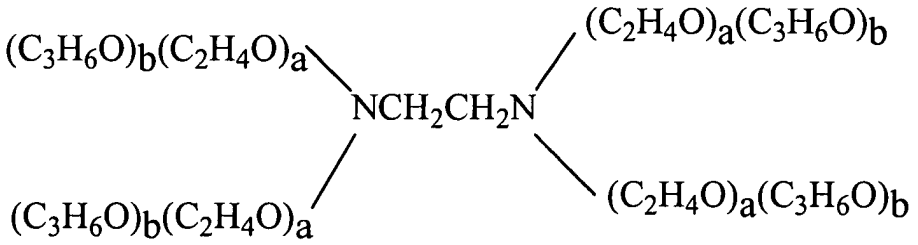
a is a number such that the portion represented by polyoxyethylene constitutes between about 5% and about 20% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes between about 80% and about 95% of the octablock copolymer by weight. See the specification at page 8, line 15-page 9, line 9; page 12, line 34-page 13, line1; page 25, lines 15-22; original Claim 17 and Table II.

Claim 38 recites a method of delivering a molecule to an animal comprising,

administering to the animal a composition comprising one or more nucleic acid sequences which encode a gene product, and

an octablock copolymer, wherein the octablock copolymer has the following formula:



wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is between about 5000 and about 7000 Daltons;

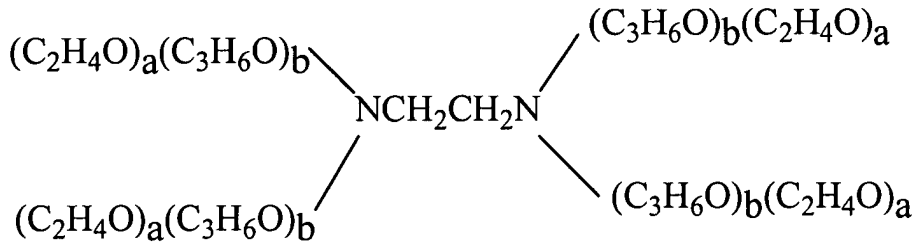
a is a number such that the portion represented by polyoxyethylene constitutes between about 10% and about 40% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes between about 60% and about 90% of the octablock copolymer by weight. See the specification at page 8, line 15-page 9, line 9; and page 9, lines 9-15 and original Claim 27.

Claim 41 recites a composition comprising,

one or more nucleic acid sequences selected from the group consisting of oligonucleotides, antisense oligonucleotides, triplex DNA compounds, ribozymes, and mixtures thereof; and

an octablock copolymer, wherein the octablock copolymer has the following formula:



wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is between about 5000 and about 7000 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes between about 5% and about 20% of the octablock copolymer by weight; and

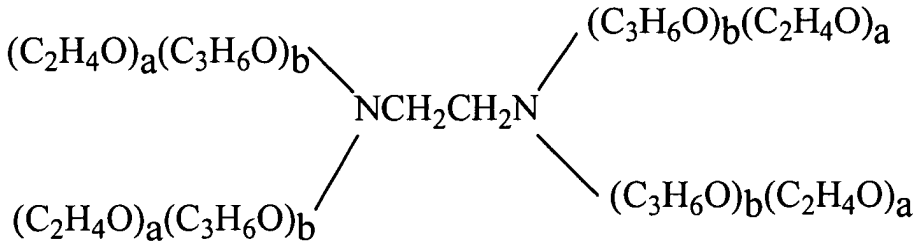
b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer is greater than 80% and less than about

95% of the octablock copolymer. See the specification at page 7, line 16-page 8, line 14; page 12, line 34-page 13, line 1; page 25, lines 15-22 and Table II.

Claim 42 recites a method of delivering a molecule to an animal comprising,

administering to the animal a composition comprising one or more nucleic acid sequences selected from the group consisting of oligonucleotides, antisense oligonucleotides, triplex DNA compounds, ribozymes, and mixtures thereof; and

an octablock copolymer, wherein the octablock copolymer has the following formula:



wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is between about 5000 and about 7000 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes less than 10% and more than about 5% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer is greater than 90% and less than about 95% of the octablock copolymer. See the specification at page 7, line 16-page 8, line 14; page 12, line 34-page 13, line 1; page 25, lines 15-22 and Table II.

VI. Ground for Rejection Presented for Review

One issue presented for review is the propriety of the Examiner's rejection of pending Claims 1-5, 8-13, 16-23, 26-31, 33-36, 38 and 41 under 35 U.S.C. §102(e) as

being anticipated by Lemieux *et al.,* (U.S. Patent 6,359,054, "Lemieux") filed January 8, 1999.

A further issue for review is the propriety of the Examiner's rejection of pending Claims 1, 6, 7, 9, 14, 15, 19, 24, 25, 27, 32 and 37 under 35 U.S.C. §103(a) as being unpatentable over Lemieux and further in view of Emanuele *et al.,* (U.S. Patent No. 5,674,911, "Emanuele") filed June 6, 1995. Applicants note that the instant application claims priority to the same priority document (U.S. patent application Ser. No. 07/673,289) as Emanuele.

Appellants also request review of the propriety of the Examiner's rejection of pending Claims 1, 2, 5, 8, 17-20, 23, 26, and 41 under 35 U.S.C. §103(a) as being unpatentable over Pahlson *et al.,* (*Acta Pathol. Microl. Immunol. Scand. B* (1986) 94(3): 117-125, "Pahlson") in view of Woodward (*Laboratory Animal Science* (1989 May) 39(3): 222-225, "Woodward").

Appellants further request review of the propriety of the Examiner's rejection of pending Claims 3, 4, 9-13, 16, 21, 22, 27-31, 33, 35, 36 and 38 under 35 U.S.C. §103(a) as being unpatentable over Pahlson and Woodward as applied above, and further in view of Jansen *et al.,* (US Patent 4,902,500, "Jansen") filed November 23, 1988.

Appellants also request review of the propriety of the Examiner's rejection of pending Claims 1-5, 8-13, 16-18, 20-22, 28-30, and 34-36 under 35 U.S.C. §103(a) as being unpatentable over Kabanov *et al.,* (US Patent 5,656,611, "Kabanov") filed November 18, 1994.

Finally, appellants request review of the propriety of the Examiner's rejection of pending Claims 17, 39, 40, and 42 under 35 U.S.C. §103(a) as being unpatentable over Lemieux.

VII. Argument

A. Introduction

Appellants' invention is directed to therapeutic delivery compositions and methods that are particularly suited for the effective delivery of genetic matter and

compounds to the interior of cells. To be successful, these technologies require an effective means for delivery of genetic-based therapeutics across cellular, nuclear and microorganism membranes. The design of a composition containing a genetic-based therapeutic and the ability to successfully deliver genetic-based therapeutics across cellular and nuclear membranes has, to date, presented a significant stumbling block to such technologies. Appellants' composition resolves this problem in a unique way.

Conventional delivery techniques of genetic material often result in the elicitation of an immune response. Typically, an immune response is mounted when the genetic material is either expressed to form gene products within the animal or human to which it was administered, or the genetic material administered is recognized simply as foreign material and destroyed. However, the conventional techniques are flawed. Without successful delivery across nuclear or cellular membranes, genetic material is destroyed before being expressed, incorporated or effectively acting as a therapeutic compound.

Triplex DNA technology provides oligonucleotides and compounds that specifically bind to regions of duplex DNA and are capable of inactivating targeted genes. However, the oligonucleotide or compound must pass through not only the cellular membrane of a cell, but also a microbial membrane when treating microbial infections or a nuclear membrane when treating eukaryotic gene function. If it were possible to administer genetic-based therapeutic compositions directly and successfully to the interior of a cell, such administration would circumvent the need to remove and treat cells *ex vivo* and also alleviate the aforementioned drawbacks regarding nuclear and cellular transportation.

In contrast to conventional techniques and compositions, appellants compositions contain genetic-based therapeutics in conjunction with an octablock copolymer of specific polyoxyethylene and polyoxypropylene portions that allow the compositions to transverse both nuclear and cellular membranes. Advantageously, the compositions facilitate transportation and therefore, delivery of a genetic-based therapeutic to the interior of cells.

Four substantive Office Actions have issued for the present application. The Examiner has withdrawn a prior Restriction Requirement and has withdrawn rejections under 35 U.S.C. §112, second paragraph. The Examiner has issued a final rejection of the pending claims over the cited prior art.

B. Independent Claims 1, 8, 9, 16, 17 19, 26, 27, 33, 38, 41 and 42 (Grouped With Claims 2-7, 10-15, 18, 20-25, 28-32, 34-37 and 39-40).

Appellants maintain that all of the pending claims of the present application are fully entitled to a priority date of at least October 15, 1993, which renders Lemieux, Emanuele, and Kabanov invalid as §102(b) or §103(a) references.

The present application claims priority to U.S.S.N. 08/138,271, filed October 15, 1993, (hereinafter the '271 application) and U.S.S.N. 07/673,289, filed March 19, 1991, (hereinafter the '289 application). The Examiner asserts that the subject matter of the pending claims is not supported by the disclosure set forth in the priority documents.

The focus of the '271 application is the introduction of drugs and other therapeutic compounds to the interior of cells. The '271 application teaches the use of polymers to introduce nucleic acids and genetic material into cells and across cellular membranes (see page 6, lines 1-4; page 6, lines 23-28; page 7, lines 9-13; page 7, lines 14-18 and page 8, lines 23-29 of U.S.S.N. 08/138,271). While, the '271 application exemplifies the use of linear polymers, the specification is clearly not limited to linear polymers. Indeed, Appellants incorporated into the specification by reference the polymers taught by Schmolka *et al.* (*J. Am. Oil Chemist Soc.* 54:110-116 (1977), hereinafter "Schmolka") and U.S. Patent No. 2,674,619 to Lundsted (hereinafter the Lundsted patent) (see page 15, lines 20-23 and page 17, lines 12-18 of U.S.S.N. 08/138,271). Both Schmolka and Lunsted teach octablock copolymers. Therefore, the '271 application clearly teaches polymers as a delivery system to introduce nucleic acid sequences or compounds capable of altering nucleic acid sequence function into cells and methods of delivering these compositions.

The '271 application incorporates by reference the Lundsted patent in accordance with MPEP §608.01(p). Therefore, the Lundsted patent is clearly **incorporated by reference in its entirety**. (See page 15, lines 20-23; page 17, lines 12-18, of the '271 application). The Lundsted patent discloses octablock copolymers. (See column 2, line 50-column 4, line 27 of the Lundsted patent). In addition, Example 5 of the Lundsted patent discloses use of ethylene diamine as the base compound (Y) (see column 11, lines 11-19). Therefore, the claims of the present application are entitled to a priority date of at least October 15, 1993.

Section 608.01(p) of the MPEP clearly permits the incorporation of "essential material" by reference to a U.S. Patent. Essential material is defined as that which is necessary to describe the claimed invention, provide an enabling disclosure or describe the best mode. (MPEP §608.01(p)(I)(A)). An application is entitled to rely upon the filing date of an earlier application, even if the earlier application itself incorporates essential material by reference to another document. (MPEP §608.01(p)(I)(B), citing *Ex parte Maziere*, 27 USPQ2d 1705, 1706-07 (Bd. Pat. App. & Inter. 1993)).

In addition, the '271 application (see page 21 and 23) incorporates by reference the scientific article of Schmolka *et al.* (*J. Am. Oil Chemist Soc.* 54:110-116 (1977)). As acknowledged by the Examiner, Schmolka teaches the synthesis of block polymer non-ionic surfactants including the octablock copolymers shown in Figure 4. Appellants and others of ordinary skill in the art have relied upon Schmolka for the disclosure of octablock copolymers. Indeed, both U.S. Patent Nos. 6,440,743 and 5,656,611 to Kabanov *et al.* disclose Schmolka for the disclosure of octablock copolymers. Both U.S. Patent Nos. 6,440,743 and 5,656,611 were cited by the Examiner in previous Office Actions and are of record in the present application. Specifically, Formula XVII (column 13, line 21-column 14, line 12) of U.S. Patent No. 6,440,743, describes that an octablock copolymer is synthesized as directed by Schmolka. Similarly, Formula XVII (column 7, line 53-column 8, line 11) of U.S. Patent No. 5,656,611 describes synthesis of an octablock copolymer as directed by Schmolka.

Section 608.01(p) of the MPEP clearly permits the incorporated by reference of non-patent publications such as the Schmolka article. Appellants are willing

to amend the specification of the present application to include the material incorporated by reference as permitted by MPEP §608.01(p). However in the Advisory Action mailed February 24, 2005, the Examiner stated that such an amendment would result in the addition of new matter. Appellants assert that the material incorporated by reference would not be new matter if inserted into the present specification. Section §2163.07(b) of the MPEP provides that an application may attempt to incorporate the content of another document or part thereof by reference to the document in the text of the specification. The information incorporated in this way is considered to be as much a part of the application as filed as if the text was repeated in the application, and it should be treated as part of the text of the application as filed. "**Replacing the identified material incorporated by reference with the actual text is not new matter.**" (MPEP §2163.07(b), emphasis added. See also, *In re Hawkins*, 486 F.2d 569 (CCPA 1973)).

Additionally, appellants have complied with the requirements under 37 C.F.R. §1.57(b) that an incorporation by reference must be set forth in the specification and must:

(1) express a clear intent to incorporate by reference by using the root words "incorporate" and "reference" (e.g., "incorporate by reference"); and

(2) clearly identify the referenced patent application or publication.

Appellants clearly expressed the intent to incorporate both the Lundsted patent and the Schmolka *et al.* publication by reference as identified on page 15, lines 20-23; page 17, lines 12-18 of the '271 application as filed; pages 21- 23 of the '271 application and page 23, lines 13-17 of the '289 application as filed.

Appellants respectfully submit that the present application discloses nucleic acid sequences in combination with octablock copolymers and therefore correctly claims priority for the currently claimed combination. For at least the foregoing, appellants submit they have complied with 37 C.F.R. §1.57 and respectfully request a priority date of at least October 15, 1993 for pending Claims 1-42.

C. Independent Claims 1, 8, 9, 16, 17, 19, 26, 27, 33, 38 and 41 (Grouped With Claims 2-5, 10-13, 18, 20-23, 28-31 and 35-36).

Appellants maintain that the pending claims of the present application are novel and non-obvious over the prior art references of Pahlson and Woodard.

The Examiner asserts that Pahlson teaches a method of **inducing an immune response** in mice by administering whole bacteria emulsified in Freund's complete adjuvant. The Examiner states whole bacteria are considered to be expression vectors with sequences that can alter the function of nucleic acids. Pahlson does not teach an octablock copolymer.

The Examiner asserts that Woodward teaches a copolymer, T1501, that is equivalent to Freund's complete adjuvant **for the purpose of stimulating antibody production** (see Office Action mailed December 1, 2004, page 9). The Examiner concludes it would be obvious to one of ordinary skill in the art at the time of the invention to substitute the T1501 copolymer of Woodward for the Freund's complete adjuvant of Pahlson, and that one would be motivated to do so because Woodward teaches that T1501 and Freud's complete adjuvant are equivalent in the art of **stimulating antibody production**.

Contrary to the Examiner's assertion, the pending claims are **not directed to a method of inducing antibody production or to a method for enhancing an immune response**. In contrast, the pending claims are directed to a method of delivering a molecule to an animal comprising one or more nucleic acid sequences, selected from the group consisting of oligonucleotides, antisense oligonucleotides, triplex DNA compounds, ribozymes and mixtures thereof, and an octoblock copolymer. Claims 26 and 38 are directed to a method of delivering a molecule to an animal comprisin, one or more nucleic acid sequences, which encode a gene product, and an octoblock copolymer.

Pahlson and Woodward fail to suggest, teach or motivate one of ordinary skill in the art to derive the claimed invention. Based on the teachings of Pahlson and Woodward, even if one were to combine the above teachings, the method would result in the induction of an immune response or stimulation of antibody production. In contrast, Pahlson and Woodward fail to teach the successful delivery of oligonucleotides, antisense oligonucleotides, triplex DNA compounds, ribozymes across cellular and plasma membranes as demonstrated in the present application. The Examiner suggests whole

bacteria are "expression vectors" and that whole bacteria contain "oligonucleotides" and "antisense oligonucleotides". Appellants wish to point out that bacterial DNA is **unmethylated**, which is why the introduction of whole bacteria to mice as demonstrated in Pahlson resulted in the elicitation of an immune response (i.e. the identification of foreign material). In contrast, mammalian DNA is methlyated and would not therefore result in the elicitation of an immune response. The elicitation of an immune response does not teach, indicate or suggest that nucleic acid sequences capable of altering nucleic acid sequence function were successfully delivered across cellular or plasma membranes, but that the material introduced to the host and was recognized as foreign material. Appellants submit that the Examiner's generalizations regarding whole bacterial are inaccurate. Therefore, the invention as a whole is not *prima facie* obvious in view of Pahlson and Woodward.

Appellants maintain that the pending claims of the present application are novel and non-obvious over the prior art references of Pahlson, Woodard and Jansen.

The teachings of Pahlson and Woodward are summarized above. Pahlson and Woodward fail to teach the octablock copolymers of Claims 3, 4, 9-13, 16, 21, 22, 27-31, 33, 35, 36 and 38. The Examiner asserts that Jansen teaches octablock copolymers T1301, T1101, T150R1, T130R2, and T110R1 and that it would be obvious to one of ordinary skill in the art to substitute the Freund's complete adjuvant of Pahlson for one of Jansen's octablock copolymers.

As stated above, the pending claims are **not directed to a method of inducing antibody production or to a method for enhancing an immune response**. In contrast, the pending claims are directed to a method of delivering a molecule to an animal comprising one or more nucleic acid sequences, selected from the group consisting of oligonucleotides, antisense oligonucleotides, triplex DNA compounds, ribozymes and mixtures thereof, and an octoblock copolymer. Claims 26 and 38 are directed to a method of delivering a molecule to an animal comprising one or more nucleic acid sequences, which encode a gene product, and an octoblock copolymer.

Pahlson, Woodward and Jansen fail to suggest, teach or motivate one of ordinary skill in the art to derive the claimed invention. Based on the teachings of

Pahlson, Woodward and Jansen even if one were to combine the above teachings, the method would only result in the **induction of an immune response or stimulation of antibody production.** In contrast, Pahlson, Woodward and Jansen fail to teach the successful delivery of oligonucleotides, antisense oligonucleotides, triplex DNA compounds, ribozymes across cellular and plasma membranes as demonstrated in the present application. The Examiner suggests whole bacteria are "expression vectors" and that whole bacteria contain "oligonucleotides" and "antisense oligonucleotides". However, bacterial DNA is **unmethylated,** which is why the introduction of bacterial DNA to mice as demonstrated in Pahlson resulted in the elicitation of an immune response (i.e. the identification of foreign material). In contrast, mammalian DNA is methlyated and would not therefore result in the elicitation of an immune response. Therefore, the Examiner's generalizations regarding whole bacterial are inaccurate and not applicable. Furthermore, the delivery of oligonucleotides, antisense oligonucleotides, triplex DNA compounds, ribozymes or mixtures thereof, is not taught or suggested by Jansen or Woodward.

Appellants respectfully submit that that the invention as a whole is not *prima facie* obvious in view of Pahlson, Woodward and Jansen.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The pending claims of the application on appeal are not directed to a method for the production of antibodies or the elicitation of an immune response. There is no reasonable expectation of success and thus no *prima facie* case of obviousness

regarding a method of delivering nucleic acids using the octablock copolymers as claimed in the present application.

In determining the differences between the prior art and the claims, the question under 35 U.S.C. §103 is not whether the differences **themselves** would have been obvious, but whether the claimed invention **as a whole** would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983) (Claims were directed to a vibratory testing machine (a hard-bearing wheel balancer) comprising a holding structure, a base structure, and a supporting means which form "a single integral and gaplessly continuous piece." *Nortron* argued the invention is just making integral what had been made in four bolted pieces, improperly limiting the focus to a structural difference from the prior art and failing to consider the invention as a whole. The prior art perceived a need for mechanisms to dampen resonance, whereas the inventor eliminated the need for dampening via the one-piece gapless support structure. "Because that insight was contrary to the understandings and expectations of the art, the structure effectuating it would not have been obvious to those skilled in the art." 713 F.2d at 785, 218 USPQ at 700 (citations omitted).). See also *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) (Claims were directed to a three step process for preparing sweetened foods and drinks. The first two steps were directed to a process of producing high purity maltose (the sweetener), and the third was directed to adding the maltose to foods and drinks. The parties agreed that the first two steps were unobvious but formed a known product and the third step was obvious. The Solicitor argued the preamble was directed to a process for preparing foods and drinks sweetened mildly and thus the specific method of making the high purity maltose (the first two steps in the claimed process) should not be given weight, analogizing with product-by-process claims. The court held "due to the admitted unobviousness of the first two steps of the claimed combination of steps, the subject matter as a whole would not have been obvious to one of ordinary skill in the art at the time the invention was made." 535 F.2d at 69, 190 USPQ at 17 (emphasis in original). The preamble only recited the purpose of the process and did not limit the body of the

claim. Therefore, the claimed process was a three step process, not the product formed by two steps of the process or the third step of using that product.).

Appellants submit that the claimed invention as a whole is non-obvious over Jansen, Woodward and Pahlson. None of these references, alone or in combination, describe the claimed nucleic acid and octablock copolymer composition. Furthermore, none of these references, alone or in combination, teach a method of delivering nucleic acids using an octablock copolymer composition.

VIII. Claims Appendix

A copy of the claims involved in this appeal is attached hereto as Appendix A.

IX. Evidence Appendix

A copy of the Schmolka and Lundsted references are provided herein. The Lundsted patent is incorporated by reference in its entirety in the '271 application as filed (see page 15, lines 20-23; and page 17, lines 12-18). Schmolka is cited in the '271 application as filed (see page 17, lines 12-18) and was previously submitted in the Information Disclosure Statement filed with the U.S. Patent Office and entered by the Examiner on January 5, 2001.

X. Related Proceedings Appendix

Not applicable to this appeal.

Conclusion

For at least the foregoing reasons, appellants request that the Examiner's rejection be reversed and that Claims 1-42 be allowed.

Respectfully submitted,

Zara A. Doddridge, PhD.
Limited Reg. No. L0030

KILPATRICK STOCKTON LLP
1100 Peachtree Street, Suite 2800
Atlanta, Georgia 30309
Telephone: 404-815-6500
Our Docket No.: 19720-0625 (42896-261843)

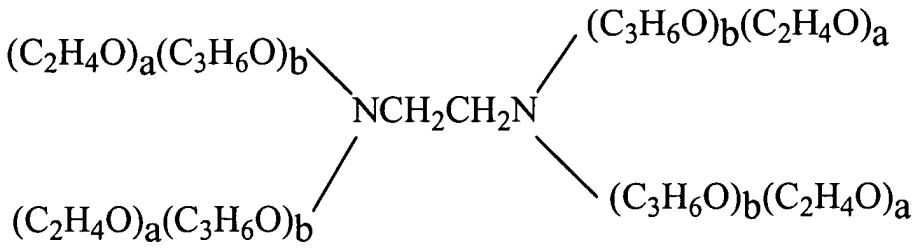
APPENDIX A

(CLAIMS INVOLVED IN THE APPEAL)

1. A composition comprising,

one or more nucleic acid sequences selected from the group consisting of oligonucleotides, antisense oligonucleotides, triplex DNA compounds, ribozymes, and mixtures thereof; and

an octablock copolymer, wherein the octablock copolymer has the following formula:



wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is between about 5000 and about 7000 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes between about 10% and about 40% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes between about 60% and about 90% of the octablock copolymer by weight.

2. The composition of Claim 1, wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is about 6750 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes about 10% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes about 90% of the octablock copolymer by weight.

3. The composition of Claim 1, wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is about 5750 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes approximately 10% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes about 90% of the octablock copolymer by weight.

4. The composition of Claim 1, wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is about 5220 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes about 10% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes about 90% of the octablock copolymer by weight.

5. The composition of Claim 1, wherein the one or more nucleic acid sequences are antisense oligonucleotides.

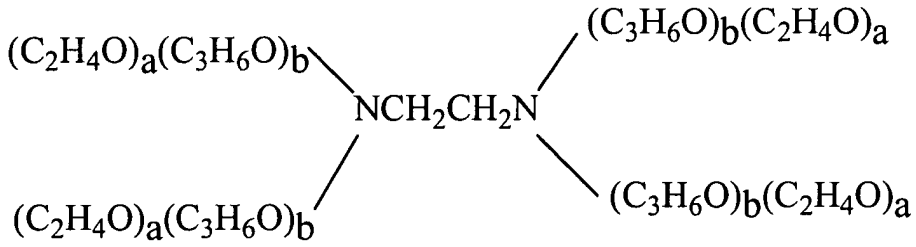
6. The composition of Claim 1, further comprising approximately 0.1% to approximately 5% by weight of a surfactant and approximately 0.5% to approximately 5% by volume of a low molecular weight alcohol.

7. The composition of Claim 6, wherein the surfactant is polyoxyethylene (20) sorbitan monooleate and the alcohol is ethanol.

8. A composition comprising,

one or more nucleic acid sequences which encode a gene product; and

an octablock copolymer, wherein the octablock copolymer has the following formula:



wherein:

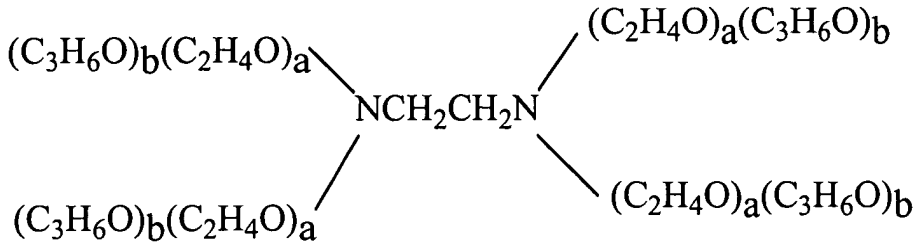
the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is between about 5000 and about 7000 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes between about 10% and about 40% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes between about 60% and about 90% of the octablock copolymer by weight.

9. A composition comprising,

one or more nucleic acid sequences selected from the group consisting of oligonucleotides, antisense oligonucleotides, triplex DNA compounds, ribozymes, and mixtures thereof; and an octablock copolymer, wherein the octablock copolymer has the following formula:



wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is between about 5000 and about 7000 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes between about 10% and about 40% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes between about 60% and about 90% of the octablock copolymer by weight.

10. The composition of Claim 9, wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is about 6750 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes about 10% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes about 90% of the octablock copolymer by weight.

11. The composition of Claim 9, wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is about 5750 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes approximately 10% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes about 90% of the octablock copolymer by weight.

12. The composition of Claim 9, wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is about 5220 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes about 10% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes about 90% of the octablock copolymer by weight.

13. The composition of Claim 9, wherein the one or more nucleic acid sequences are antisense oligonucleotides.

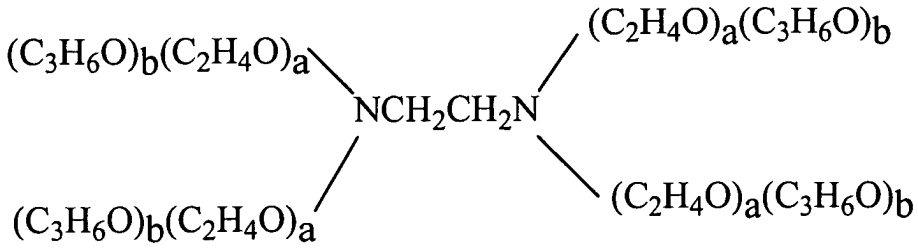
14. The composition of Claim 9, further comprising approximately 0.1% to approximately 5% by weight of a surfactant and approximately 0.5% to approximately 5% by volume of a low molecular weight alcohol.

15. The composition of Claim 14, wherein the surfactant is polyoxyethylene (20) sorbitan monooleate and the alcohol is ethanol.

16. A composition comprising,

one or more nucleic acid sequences which encode a gene product; and

an octablock copolymer, wherein the octablock copolymer has the following formula:



wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is between about 5000 and about 7000 Daltons;

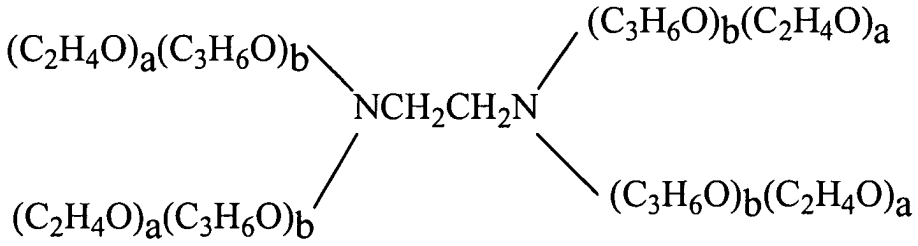
a is a number such that the portion represented by polyoxyethylene constitutes between about 10% and about 40% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes between about 60% and about 90% of the octablock copolymer by weight.

17. A composition comprising,

one or more nucleic acid sequences selected from the group consisting of oligonucleotides, antisense oligonucleotides, triplex DNA compounds, ribozymes, and mixtures thereof; and

an octablock copolymer, wherein the octablock copolymer has the following formula:



wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is between about 5000 and about 7000 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes between about 5% and about 20% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes between about 80% and about 95% of the octablock copolymer by weight.

18. The composition of Claim 17, wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is about 6750 Daltons;

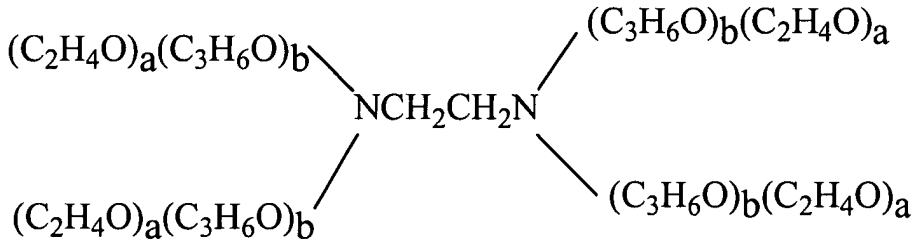
a is a number such that the portion represented by polyoxyethylene constitutes about 10% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes about 90% of the octablock copolymer by weight.

19. A method of delivering a molecule to an animal comprising,

administering to the animal a composition comprising one or more nucleic acid sequences selected from the group consisting of oligonucleotides, antisense oligonucleotides, triplex DNA compounds, ribozymes, and mixtures thereof; and

an octablock copolymer, wherein the octablock copolymer has the following formula:



wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is between about 5000 and about 7000 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes between about 10% and about 40% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes between about 60% and about 90% of the octablock copolymer by weight.

20. The method of Claim 19, wherein

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is about 6750 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes about 10% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes about 90% of the octablock copolymer by weight.

21. The method of Claim 19, wherein

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is about 5750 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes approximately 10% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes about 90% of the octablock copolymer by weight.

22. The method of Claim 19, wherein

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is about 5220 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes about 10% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes about 90% of the octablock copolymer by weight.

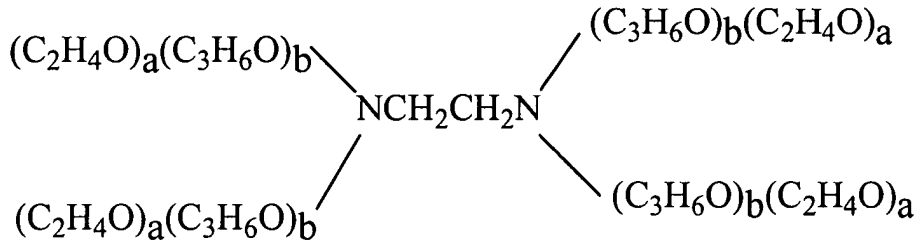
23. The method of Claim 19, wherein the one or more nucleic acid sequences are antisense oligonucleotides.

24. The method of Claim 19, wherein the composition further comprises approximately 0.1% to approximately 5% by weight of a surfactant and approximately 0.5% to approximately 5% by volume of a low molecular weight alcohol.

25. The method of Claim 24, wherein the surfactant is polyoxyethylene (20) sorbitan monooleate and the alcohol is ethanol.

26. A method of delivering a molecule to an animal comprising,

administering to the animal a composition comprising one or more nucleic acid sequences which encode a gene product, and an octablock copolymer, wherein the octablock copolymer has the following formula:



wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is between about 5000 and about 7000 Daltons;

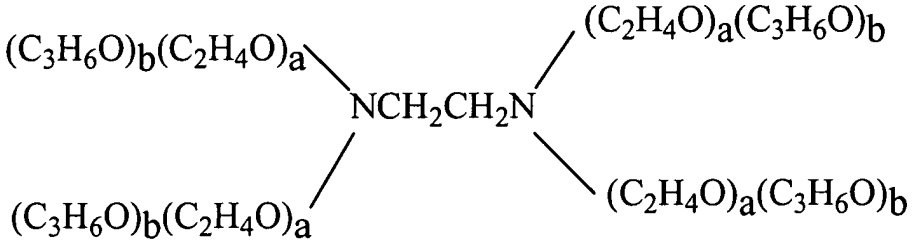
a is a number such that the portion represented by polyoxyethylene constitutes between about 10% and about 40% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes between about 60% and about 90% of the octablock copolymer by weight.

27. A method of delivering a molecule to an animal comprising,

administering to the animal a composition comprising one or more nucleic acid sequences selected from the group consisting of oligonucleotides, antisense oligonucleotides, triplex DNA compounds, ribozymes, and mixtures thereof; and

an octablock copolymer, wherein the octablock copolymer has the following formula:



wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is between about 5000 and about 7000 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes between about 10% and about 40% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes between about 60% and about 90% of the octablock copolymer by weight.

28. The method of Claim 27, wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is about 6750 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes about 10% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes about 90% of the octablock copolymer by weight.

29. The method of Claim 27, wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is about 5750 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes approximately 10% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes about 90% of the octablock copolymer by weight.

30. The method of Claim 27, wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is about 5220 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes about 10% of the octablock copolymer by weight; and

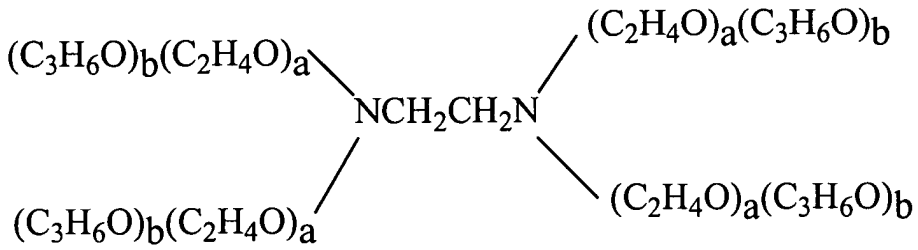
b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes about 90% of the octablock copolymer by weight.

31. The method of Claim 27, wherein the one or more nucleic acid sequences are antisense oligonucleotides.

32. The method of Claim 27, wherein the composition further comprises approximately 0.1% to approximately 5% by weight of a surfactant and approximately 0.5% to approximately 5% by volume of a low molecular weight alcohol.

33. A method of delivering a molecule to an animal comprising,

administering to the animal one or more nucleic acids sequences selected from the group consisting of oligonucleotides, antisense oligonucleotides, triplex DNA compounds, ribozymes, and mixtures thereof; and an octablock copolymer, wherein the octablock copolymer has the following formula:



wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is between about 5000 and about 7000 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes between about 5% and about 20% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes between about 80% and about 95% of the octablock copolymer by weight.

34. The method of Claim 33, wherein

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is about 6750 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes about 10% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes about 90% of the octablock copolymer by weight.

35. The method of Claim 33, wherein

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is about 5750 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes approximately 10% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes about 90% of the octablock copolymer by weight.

36. The method of Claim 33, wherein

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is about 5220 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes about 10% of the octablock copolymer by weight; and

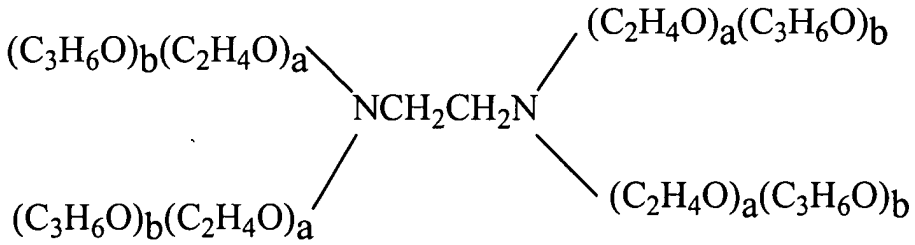
b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes about 90% of the octablock copolymer by weight.

37. The method of Claim 32, wherein the surfactant is polyoxyethylene (20) sorbitan monooleate and the alcohol is ethanol.

38. A method of delivering a molecule to an animal comprising,

administering to the animal a composition comprising one or more nucleic acid sequences which encode a gene product, and

an octablock copolymer, wherein the octablock copolymer has the following formula:



wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is between about 5000 and about 7000 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes between about 10% and about 40% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer constitutes between about 60% and about 90% of the octablock copolymer by weight.

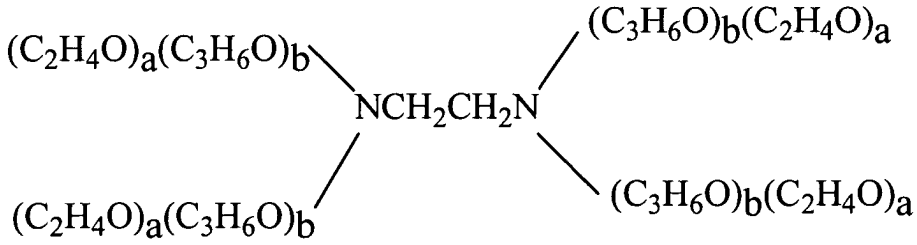
39. The composition of Claim 17, wherein the polyoxypropylene portion of the total molecular weight of the octablock copolymer is greater than 90% and less than about 95%.

40. The method of Claim 33, wherein the polyoxypropylene portion of the total molecular weight of the octablock copolymer is greater than 90% and less than about 95%.

41. A composition comprising,

one or more nucleic acid sequences selected from the group consisting of oligonucleotides, antisense oligonucleotides, triplex DNA compounds, ribozymes, and mixtures thereof; and

an octablock copolymer, wherein the octablock copolymer has the following formula:



wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is between about 5000 and about 7000 Daltons;

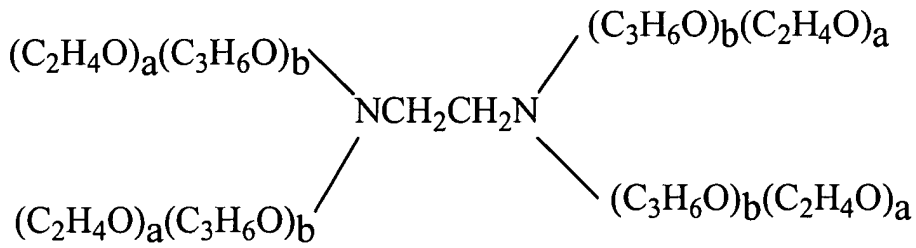
a is a number such that the portion represented by polyoxyethylene constitutes between about 5% and about 20% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer is greater than 80% and less than about 95% of the octablock copolymer.

42. A method of delivering a molecule to an animal comprising,

administering to the animal a composition comprising one or more nucleic acid sequences selected from the group consisting of oligonucleotides, antisense oligonucleotides, triplex DNA compounds, ribozymes, and mixtures thereof; and

an octablock copolymer, wherein the octablock copolymer has the following formula:



wherein:

the mean aggregate molecular weight of the portion of the octablock copolymer represented by polyoxypropylene is between about 5000 and about 7000 Daltons;

a is a number such that the portion represented by polyoxyethylene constitutes less than 10% and more than about 5% of the octablock copolymer by weight; and

b is a number such that the polyoxypropylene portion of the total molecular weight of the octablock copolymer is greater than 90% and less than about 95% of the octablock copolymer.

Reprinted from the JOURNAL OF THE AMERICAN OIL CHEMISTS' SOCIETY, V. 54, No. 3, Pages: 110-116 (1977)

A Review of Block Polymer Surfactants

EXHIBIT A

IRVING R. SCHMOLKA, BASF Wyandotte Corp., Wyandotte, MI 48192

ABSTRACT AND SUMMARY

A brief historical review of four series of commercially available block polymer surface-active agents—the PLURONIC[R], TETRONIC[R], PLURADOT[R], and PLURONIC[R] R polyols—is presented. A comparison is made of the physical properties within each series, in the form of trend lines. These parameters encompass solubility, rate of solubility, wetting, foaming, defoaming, emulsification, thickening, cleansing, and toxicity. The physical property relationships which depend upon variation in the hydrophobe molecular weight and variation in the hydrophile hydrophobe balance are shown to be similar in each series of surfactants. Differences among the four series of polymers, where they exist, are seen to vary from little to significant. The many controversial articles on the micellar nature of the block polymers and their critical micelle concentrations are examined. Considerations of the important physical properties which lead to practical applications are discussed. Some of the more important newly developed potential uses of these polymeric surfactants are then described in various application areas, including the cosmetic, medical, paper, pharmaceutical, and textile industries.

INTRODUCTION

A block polymer nonionic surfactant is a surface active agent prepared by the sequential addition of two or more alkylene oxides to a low molecular weight water-soluble organic compound containing one or more active hydrogen atoms. It is the purpose of this review to compare the physical properties of four different groups of commercially available block polymer surfactants and to discuss some of their most recent industrial applications. The block polymer surfactants to be reviewed include the PLURONIC[R], PLURONIC[R] R, TETRONIC[R], and the PLURADOT[R] polyols. The corresponding nonproprietary names of the first three are poloxamer, meroxapol, and poloxamine, (1) respectively.

SYNTHESIS

The poloxamers are synthesized (2) by the sequential addition first of propylene oxide and then ethylene oxide to a low molecular weight water-soluble organic compound, propylene glycol. The hydrophobe is the inner polyoxypropylene glycol which changes from a water soluble- to a water insoluble- polymer as the molecular weight goes above 750. The addition of ethylene oxide in the final step provides water solubility to the molecule. In this series, as in all other syntheses to be presented, the oxyalkylation steps are carried out in the presence of an alkaline catalyst, generally sodium or potassium hydroxide. The alkaline catalyst is then neutralized and usually removed from the final product. The equations representing this synthesis are shown in Figure 1.

When the order of addition of the alkylene oxides is reversed, the meroxapol series is produced (3), as shown by the equations in Figure 2.

In this series, ethylene glycol is the initiator. It is informative to note the essential important differences between the poloxamer and the meroxapol structures. This should be kept in mind when physical properties of the two series are compared with each other. The poloxamer structure is terminated by two primary hydroxyl groups, while the meroxapol series has secondary hydroxyl groups at the ends. In the poloxamer series the hydrophobe is on the inside, while the corresponding meroxapol has the hydrophobe split in two, each half of which is on the outside of the surfactant. This is illustrated in Figure 3.

A slightly different structure is exhibited by the poloxamines, which are prepared (4) from an ethylenediamine initiator. These resemble the poloxamers in having the same sequential order of addition of alkylene oxides. Their synthesis is shown in Figure 4.

Structurally, the poloxamines differ from the other polymers in that they have four alkylene oxide chains, rather than two, since four active hydrogens are present in the initiator. These surfactants also differ from the other polymers in that they contain two tertiary nitrogen atoms, at least one of which is capable of forming a quaternary salt (5). These polymers are also terminated by primary hydroxyl groups.

The fourth series of surfactants to be discussed are the PLURADOT polyols. Currently there is no nonproprietary name assigned to this family of polymers. These surface active agents can be prepared (6) from a low molecular weight trifunctional alcohol, such as glycerine or trimethyl-

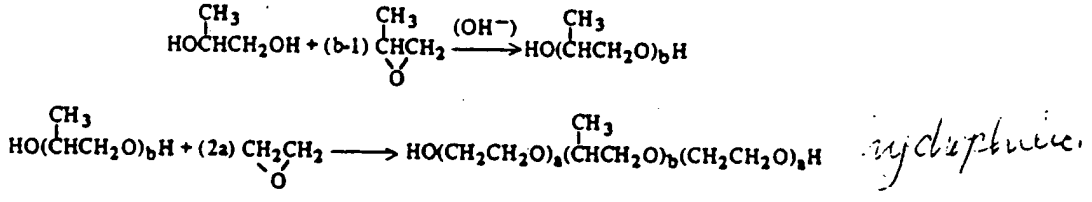


FIG. 1. Poloxamer Synthesis

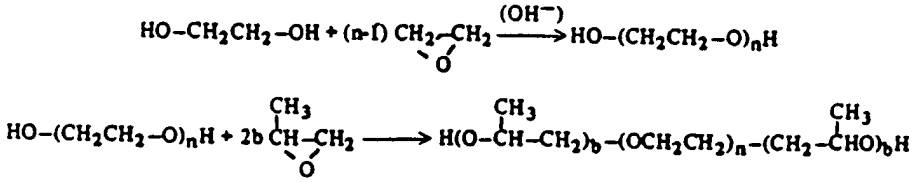
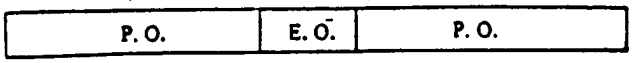


FIG. 2. Meroxapol Synthesis

Meroxapol



Poloxamer

FIG. 3.

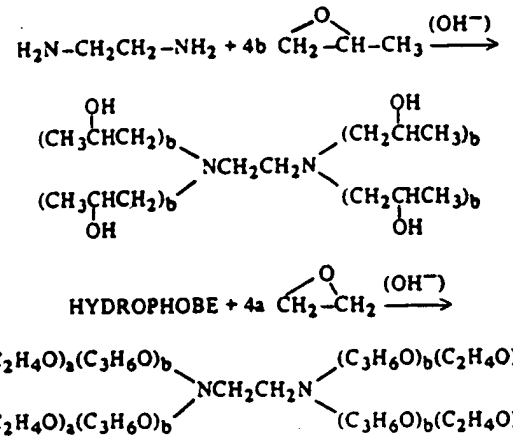


FIG. 4. Poloxamine Synthesis

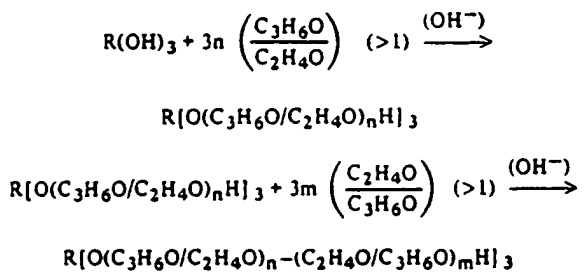


FIG. 5. Pluradot Polyol Synthesis

olpropane, which is oxyalkylated initially with a blend of propylene and ethylene oxides, but mostly with propylene oxide, to form the hydrophobe. This is followed by oxyalkylating with a blend of ethylene and propylene oxides, but mostly with ethylene oxide, to form a hydrophile. This synthesis scheme is shown in Figure 5.

This group of surfactants has three chains, one more than the poloxamer and meroxapol series, but one less than the poloxamine polymers. Because of the slower rate of reaction of propylene oxide, compared to ethylene oxide, it is suggested that the terminal hydroxyl group is composed primarily of secondary hydroxyl groups rather than of primary hydroxyl groups.

Obviously there are no chemical differences within any one series of polymeric surfactants. Among the four series, there are two differences. (1) The presence of the two tertiary nitrogen atoms in the poloxamines and their absence in the other polymers, and (2) the terminal secondary or primary hydroxyl groups, as mentioned previously.

NOMENCLATURE

Since there are more than seventy-five different polymeric surfactants, the nomenclature of each system will be explained. As seen in Table I, which illustrates the poloxamer series, the first two digits of a poloxamer, when multiplied by 100, indicate the approximate hydrophobe molecular weight. The last digit, when multiplied by 10, gives the percent of ethylene oxide in the molecule, the balance being propylene oxide.

The meroxapol series is shown in Table II. The first two digits, when multiplied by 100, give the total molecular weight of the two polyoxpropylene glycol hydrophobes. The last digit, multiplied by 10, gives the percent ethylene oxide in each polymer. In this respect the meroxapol nomenclature system resembles the poloxamer system.

The poloxamine series is described in Table III. The same system is used with the poloxamines as with the previous two series. The last digit, multiplied by 10, gives the percent ethylene oxide in the final molecule, while the first two digits are indicative of the hydrophobe molecular weight. The zero was included so as to minimize confusion with the poloxamer numbering system.

The last series, the PLURADOT polymers, is shown in Table IV.

The exact relative percentages of ethylene and propylene oxides in the hydrophobe and the hydrophile in this series are proprietary information. However, from physical property data, specifically cloud points, it can be seen that the larger the second digit, the greater is the total percent of ethylene oxide in the molecule. As seen in the table, the larger the first digit, the greater is the hydrophobe molecular weight.

PHYSICAL PROPERTIES

Cloud Point

Major differences in physical properties are seen to exist within any one series. In addition, when one compares one series with another, some differences and some similarities are readily apparent. All four nonionic series are alike in that they derive their solubility in water from hydrogen bond formation between the many ether oxygen atoms present and protons in the water. When the temperature of a solution of a nonionic surfactant is raised, the hydrogen bond is broken and the nonionic clouds out of solution. This is known as the cloud point. For poloxamers, the 1% cloud point ranges from a low of 14 C to a high of 100 C. This latter figure is for the most hydrophilic polymers containing 80% ethylene oxide. In contrast, the meroxapols have a narrower cloud point range. The important difference would be the lowered cloud point with the most hydrophilic members, those that contain 80% ethylene oxide. The poloxamines resemble the poloxamers in this property, since they are structurally similar. The PLURADOT polymers have the lowest maximum cloud point primarily because the most hydrophilic members have a lower ethylene oxide content than the 80% exhibited by the other series, and perhaps, partly due to the presence of some propylene oxide in the terminal hydrophile. These data are shown in Table V.

Water Solubility

Within any one series, as the percent of ethylene oxide increases, or the molecular weight of the hydrophobe decreases, the solubility in water increases. This is true for all four series.

Within any one series, the rate of solubility of a polymer in water decreases as the hydrophobe molecular weight increases. In a comparison of the rate of solubility in water of two similar polymers, one with the hydrophile on the outside, poloxamer 188, and the other with the hydrophile on the inside, meroxapol 17R8, the latter had a faster rate of solubility than the former.

In another comparison between two polymers with a

TABLE I

Poloxamer Series

Hydrophobe molecular weight	10	20	30	40	50	60	70	80
4000	401	402	403	-	-	-	407	-
3250	331	-	333	334	335	-	-	338
2750	-	282	-	284	-	-	-	288
2250	231	-	-	234	235	-	237	238
2050	-	212	-	-	215	-	217	-
1750	181	182	183	184	185	-	-	188
1200	-	122	123	124	-	-	-	-
950	101	-	-	-	105	-	-	108

% Ethylene oxide

TABLE II

Meroxapol Series

Hydrophobe molecular weight	10	20	30	40	50	60	70	80
3100	31R1	31R2	-	31R4	-	-	-	-
2500	25R1	25R2	-	25R4	25R5	-	-	25R8
1700	17R1	17R2	-	17R4	-	-	-	17R8
1000	-	-	-	-	10R5	-	-	10R8

% Ethylene oxide

TABLE III

Poloxamine Series

Hydrophobe molecular weight	10	20	30	40	50	60	70	80
6750	1501	1502	-	1504	-	-	-	1508
5750	1301	1302	-	1304	-	-	1307	-
4750	1101	1102	-	1104	-	-	1107	-
3750	901	-	-	904	-	-	-	908
2750	701	702	-	704	-	-	707	-
1750	-	-	-	504	-	-	-	-
750	-	-	-	304	-	-	-	-

% Ethylene oxide

similar molecular weight and the same ethylene oxide/propylene oxide ratio, the tetrafunctional polymer, poloxamine 707, was found to dissolve more rapidly than the difunctional polymer, poloxamer 407. This suggests that the length of the polymer chain has an effect on the rate of solubility.

This is substantiated when one compares the rate of solubility, within any one series, of a group of polymers with the same ethylene oxide/propylene oxide ratio, but of varying molecular weight. It has been found that the larger the molecular weight of the hydrophobe, the slower is the rate of solubility.

No solubility rate comparisons have been carried out with the PLURADOT polymers.

Oil Solubility

None of the poloxamers is soluble is mineral oil. However, by placing the polypropylene glycol hydrophobe on the outside of the molecule, it is of interest to note that many of the meroxapol polymers do exhibit moderate solubility in this lipophilic solvent. The poloxamine and PLURADOT polymers are also insoluble in mineral oil. This is to be expected, since they more closely resemble the poloxamer than the meroxapol structure.

The solubility characteristics of the four series of polymers in an organic solvent, such as propylene glycol, are quite similar. The higher the hydrophobe molecular weight, the less soluble is the polymer. Also, those polymers with a high percentage of ethylene oxide or a high percentage of propylene oxide, everything else being equal, are less soluble in propylene glycol than those polymers which have an ethylene oxide content of between 40 and 60%.

TABLE IV

Pluradot HA Series

Increasing hydrophobe molecular weight ↑	Low				High
	510	520	530	540	550
	410	420	430	440	450

% Ethylene oxide

TABLE V

1% Cloud Point, °C

Surfactant	Minimum	Maximum	Δ
Poloxamer	14	100	86
Meroxapol	25	99	74
Poloxamine	15	100	85
Pluradot	25	77	52

TABLE VI

Poloxamine Wetting Times,[a] Sec.

Hydrophobe molecular weight	10	20	30	40	50	60	70	80
6750	-	51	-	84	-	-	-	>360
5750	-	30	-	48	-	-	-	-
4750	-	15	-	37	-	-	>360	-
3750	-	-	-	88	-	-	-	-
2750	-	38	-	185	-	-	-	-
1750	-	-	-	>360	-	-	-	-

% Ethylene oxide

[a]Draves test, 3 g Hook, 0.1% solution, 25 C.

TABLE VII

Meroxapol Dynamic Foam Heights, 25 C[a]

Hydrophobe molecular weight	10	20	30	40	50	60	70	80
3100	15	40	-	215	-	-	-	-
2500	40	45	-	260	125	-	-	110
1700	115	195	-	300	-	-	-	145
1000	-	-	-	-	260	-	-	125

% Ethylene oxide

[a]For 0.1% solution at 400 ml/min flow rate.

Wetting

In each of the polymer series, the same wetting trend is observed in that wetting time, as measured by the Draves test for a 0.1% solution at 25 C, decreases as the percent hydrophile decreases. Also as the molecular weight of the hydrophobe increases, the wetting time decreases. However, above a certain limit, which varies with each series, there is no decrease in the wetting time as the hydrophobe molecular weight increases. This is exemplified in Table VI, by the poloxamine series, which shows that wetting time reaches a minimum as the hydrophobe molecular weight increases from 750 to 4750 but then rises slightly as the molecular weight increases further to 6750.

Foaming

Within each series, the foam property reaches a maximum at a different ethylene oxide/propylene oxide ratio. With the meroxapols, maximum foam height, at 25 C, is at a 40:60 ethylene oxide/propylene oxide ratio, but at 49 C, the maximum shifts to a 50:50 ratio. The poloxamers exhibit maximum foam at a slightly higher ethylene oxide/propylene oxide ratio, namely 60:40, at 49 C. From data on the limited number of polymers prepared in the poloxamine series, it appears that foam is maximized between the 40:60 and 70:30 ethylene oxide/propylene oxide ratios. Foam values in the PLURADOT series increase as the cloud point of the polymer increases. However, the limited number of polymers makes it impossible to draw any valid conclusions. Foam properties of each surfactant series increase and then decrease slightly, as the hydrophobe molecular weight increases. This is exemplified in Table VII where the numbers represent millimeters of foam generated at a 400 ml/min flow rate in the dynamic foam machine for the meroxapols.

However, the biggest difference in foam properties is found in a comparison of the foam properties of the two series which have terminal hydrophile groups, the poloxamers and the poloxamines, with the meroxapols, where the hydrophobe groups are on the outside. The latter series exhibits little or no foam, even by its most hydrophilic members. As an example, a 0.1% solution of poloxamer 188 has a foam value of 600 mm at 40 C at a 400 ml/min dynamic flow rate, while its meroxapol counterpart, 17R8, has a foam height of only 44 mm, under the same conditions. Poloxamer and poloxamine foam heights appear comparable for comparable polymers. Thus, for example, poloxamer 407 has a foam value of 160 mm at a 200 ml flow rate, while poloxamine 707 has a foam value of 180 mm, under identical test conditions.

For defoaming properties, all four series resemble each other in that the highest propylene oxide/ethylene oxide ratio surfactants are very effective defoamers and no trend lines can be drawn or large differences noted. If any generalization can be drawn, it might be that the meroxapols appear to be better defoamers than their corresponding poloxamers.

EMULSIFICATION

Attempts to correlate emulsification properties with ethylene oxide/propylene oxide ratios and hydrophobe molecular weights have not been very successful. Within any one series, the higher molecular weight hydrophobes are generally better emulsifiers than their lower molecular weight homologs. Some of the poloxamers appear to be better emulsifying agents for mineral oil or fluorocarbons in aqueous systems than the meroxapol or poloxamine polymers, while several of the latter appear superior for preparing stable emulsions of glyceryl trioleate in water. However, no trend lines can be presented.

Thickening

The thickening power of each series of surfactants in water increases as the hydrophobe molecule weight increases and as the ethylene oxide/propylene oxide ratio increases.

The available data, but not shown here, indicate that the meroxapol and PLURADOT series do not form gels at any concentrations in water, whereas only 20% of either poloxamer 407 or poloxamine 1508 is needed to form a

strong gel. In comparison, a 20% solution of poloxamer 403, poloxamer 188, poloxamine 1504, or poloxamine 908 is a fluid liquid at room temperature.

Cleansing

Because of the varying nature of substrates, soils, cleaning conditions, and types of equipment used, no one trend line can be drawn which would best describe the cleaning properties of the four series of block polymer surfactants.

Toxicity

Within any one series the toxicity of a block polymer surfactant decreases as the ethylene oxide/propylene oxide ratio increases and as the molecular weight of the hydrophobe increases. This has been shown by the acute oral LD_{50} values for the poloxamine and meraxopol series. Most values are very high, generally >5 g/kg, which is at the lower limit of the slightly toxic class in the classification scheme given in Clinical Toxicology of Commercial Products (12). It is not valid to compare the toxicity of any one series with another.

Critical Micelle Concentrations (CMC)

The early published reports (13-15) on the study of micelle formation of block copolymers of ethylene and propylene oxides claimed that these surfactants did not form micelles, in contrast to the oxyethylated fatty alcohols or alkylphenols. However, Becher (16) reported that the CMC for poloxamer 182 was 2.4 wt % while Ross and Olivier (17) reported the CMC for poloxamer 184 to be 0.026 wt %. Subsequently, Williams and Graham (private communication) determined critical micelle concentrations for several of the poloxamers, using surface tension depression methods. This controversy as to whether or not the poloxamers form micelles was examined once again when Schmolka and Raymond used a differential dye absorption technique (18) and verified the existence of micelles. The values they obtained, namely that the poloxamers had critical micelle concentrations in the range of 3.0 to 11.0 μmol per liter, agreed closely with the data previously found by Williams and Graham.

At about this time, Saski and Shah (19), using three different techniques, reported considerably higher critical micelle concentration values for the poloxamers. These were 2.4, 2.2, and 0.1 wt % respectively, for poloxamers 182, 184, and 188. On the other hand, Sheth (20) reported a critical micelle concentration value for poloxamer 188 of 0.2 wt %, by means of surface tension depression.

This confusion on CMC values has been compounded even further. Thus, Anderson (21) has reported, using the same surface tension depression method, that the critical micelle concentration values for poloxamers 181, 182, and 188 were significantly lower than those previously reported. Anderson also used the differential dye absorption technique with benzopurpurin 4B and iodine methods to study this problem, but claimed that, due to interaction of the iodine and dye with the polymers, resulting in increases in absorbance, these methods would not permit a satisfactory determination of the critical micelle concentration values of the block copolymer surfactants.

Nuclear magnetic resonance has been used (22) to study the interaction of poloxamer 188 and phenol. Starting with low phenol concentrations, up to 2%, in a 10% aqueous poloxamer 188 solution, the authors reported that the phenol was associated mainly with the poloxypropylene chain. However, as the ratio of phenol to poloxamer increased, it appeared that the polyoxypropylene chain became saturated with phenol and relatively more phenol entered the polyoxyethylene chain. The authors concluded that this indicated the presence of micelles in the poloxamer phenol water system. However, they suggested that

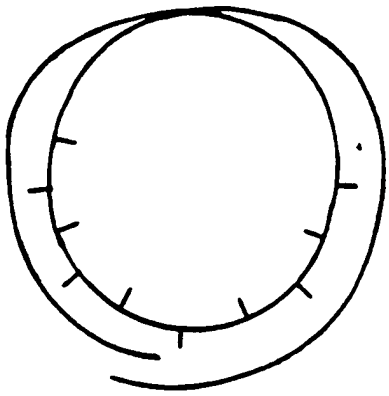


FIG. 6. Suggested poloxamer micelle configuration.

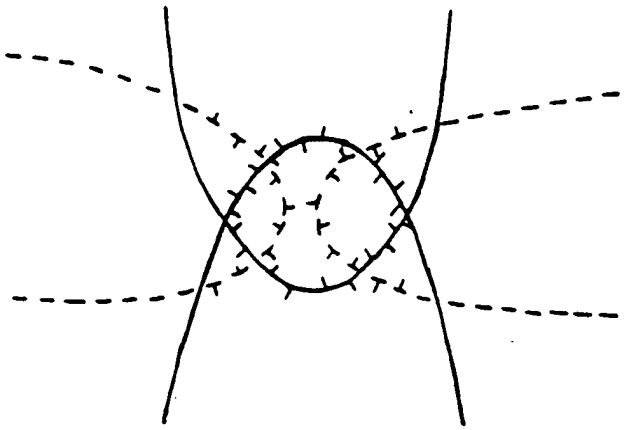


FIG. 7. Suggested poloxamer micelle configuration.

the micelle would not necessarily be aggregates of copolymer molecules as is found with other types of surfactants, but consisted of one molecule with the poloxyethylene chains rolled around the poloxypropylene region. This is illustrated in Figure 6.

The solution properties of several of the poloxamers were studied in water as well as in a nonaqueous solvent, such as benzene, dioxane, and butyl chloride. Considerable difference was found (23) between the weight and number-average molecular weight of the poloxamer micelles, as determined by light scattering and two methods of measuring vapor pressure lowering. The number of molecules per micelle found by light scattering varied, for example, for poloxamer 188, from 1.5 to 8 in the various solvents and less widely for poloxamers 108 and 338. The authors concluded that the poloxamers with a molecular weight below 2000, such as 101 and 105, failed to associate in benzene whereas higher molecular weight homologs, such as poloxamers 108 and 188, did.

In order to meet the requirements of 2-8 molecules per micelle, it is suggested that each surfactant molecule is shaped like a horseshoe, and that 2-8 interlocking horseshoe-shaped molecules form a micelle, as illustrated in Figure 7.

The solid lines represent the molecules which lie in the plane of the paper, while those represented by a dotted line are below and above the plane of the paper. On the other hand, the micellar molecular weight of poloxamer 188, as determined by light scattering, has been reported (24) to be 10^5.

Two of the poloxamines have been reported to exhibit micelles. Poloxamine 707 was found (18) to exhibit a critical micelle concentration of 0.005 wt % at 25 C, using the differential dye absorption technique. On the other

hand, the CMC value for poloxamine 908 was found to be 0.06 wt %, using both surface tension depression and solubility methods.

Previous measurements were carried out at 25 C. Most recently, the effects of temperature on the micellar properties of poloxamer 184 have been studied (25) over a range of temperatures by surface tension and light scattering techniques. The authors reported that at 25 C the micellar molecular weight is 2656, which is close to the molecular weight of 2900. However, at 30 C and 35 C, the authors reported aggregation numbers of 5.9 and 29.9, respectively. These results suggested to the authors that poloxamers behave differently from other nonionic surfactants. First, whereas other nonionic surfactant micellar sizes increase with temperature, with the poloxamers there may be temperature ranges within which no micelles form at all. Secondly, the authors believed that the growth of aggregates to a stable size takes place over much wider concentration ranges than for other nonionic surfactants, and lastly, the authors thought that the normal methods for determining CMC values of the poloxamers were inaccurate. Thus, one is led to conclude that the micellar nature of the block polymer surfactants and their critical micelle concentrations is a very complex and confused subject.

APPLICATION AREAS

Many new and interesting industrial applications for the block polymer nonionic surfactants have been developed, just in the past five or six years alone.

Most of these uses have been reported in publications such as magazine articles or patents and are not proprietary information. In reviewing these new applications, consideration will be given to the important physical property or properties which led to the selection of the block polymer. No attempt will be made to present a complete application picture, but rather only selected cases in just a few industries will be described.

The first application area to be reviewed will be cosmetics. Obviously, the primary reason for using block polymer surfactants here is their absence of toxicity, but in addition, other very specific physical properties are required.

A new dentifrice, designed for sensitive teeth, called PROTECT, uses poloxamer 407 because it is a gelling agent. The poloxamer/sodium citrate combination was reported (26) to have a highly significant desensitizing effect, in comparison with a control formulation of unknown composition. Another desirable property of the poloxamer in this application is its absence of any bitter taste. This is a new product currently being marketed in several locations in the United States.

An alcohol-based mouthwash was reported stabilized (27) by the addition of a poloxamer with an ethylene oxide content of >40%. The addition of the poloxamer prevents the formation of a cloudy appearance which would otherwise develop on standing. In this application, the lack of taste of the poloxamer, plus its ability to solubilize water insoluble aromatic flavors, are important considerations for its use.

In the field of aerosol antiperspirants, it has been reported (28) that the use of certain polyalkylene oxides, including certain poloxamers, would prevent the staining of clothing after repeated use of the antiperspirant formulation. The nonirritating properties, plus the solubilizing action, would be responsible for selecting the block polymer surfactants in this application. In the same type of aerosol product, the addition of a poloxamer to the formulation was reported (29) to prevent formation of lumps in storage. The dispersing properties of the poloxamer are believed to be the reasons for its selection in this application.

Many new applications in the medical field have been reported, and only a small number can be described here. The use of poloxamers with at least 50% ethylene oxide content has been reported (30) in a new process for the preparation of a stable and concentrated antiserum from human or animal plasma and serum, by fractional precipitation. At below room temperature conditions, the poloxamer selectively precipitates the protein fractions in various molecular weights. This precipitation is due to the ability of the two macromolecules, the polymeric poloxamer and the blood proteins, to form insoluble complexes at low temperatures. The complexes are then readily separated and purified.

Several poloxamines and their tetraesters have been found (31) to be useful as hypocholesterolaemic agents in animals and man. The starting poloxamines have a maximum ethylene oxide content of 30% and the hydrophobe molecular weight lies between 2250 and 3250. A dramatic reduction in blood serum cholesterol levels was reported when the polymers were regularly incorporated in the diet. It is suggested that the ability of the poloxamine or its esters to solubilize the sterol is the reason for this useful application.

The clinical use of poloxamer 188 as an emulsifying agent for a perfluorooctylbromide emulsion, useful as a radiopaque medium for contrast studies in medicine, is a relatively new development (32). The radiographs are equally as effective as, or more effective than, those obtained with organic iodide compounds and barium sulfate. The poloxamer was selected because of its ability to function as an emulsifying agent, and due to its lack of toxicity, including its nonthrombogenic properties.

In a similar application, poloxamer 188 has been the emulsifying agent of choice in the artificial blood program, for preparing stable emulsions of fluorocarbon in physiological saline (33).

An antiseptic skin cleaning formulation based upon chlorhexidine gluconate has been developed (34) containing 25% poloxamer 187. A problem is often encountered in hand wash formulations, namely that the cationic or antiseptic is inactivated in the micelles of the surfactant being used. This was eliminated by using a poloxamer as the wetting agent because, of all the nonionics tested, it exhibited the least inactivation of the chlorhexidine. The 187 grade was selected because it exhibited the highest foam. The 25% concentration was used in order to provide suitable foam viscosity and washing properties in the final product.

A method for enhancing drug or antibiotic levels in the blood has been reported (35) by oral administration of a capsule containing the drug and a poloxamer. Gastrointestinal hypomotility is induced and as a result of the delayed gastrointestinal transport, dwell time in the upper portion of the gastrointestinal tract is increased. This is desirable since drugs are preferentially absorbed in the upper G.I. tract. The properties associated with the selection of a poloxamer, which contains from 5-80% ethylene oxide, no doubt include absence of bitter taste, lack of toxicity, and its rate of solubility.

The effective control of bloat in beef cattle during feeding lot fattening, was reported (36) to be controlled when the cattle were fed a high concentration of a feed lot bloat inducing ration for an extended period of time and concurrently fed a bloat controlling compound, such as poloxamine 1501 or PLURADOT HA 520, together with a water soluble salt of a dimethyldialkyl quaternary ammonium compound.

Poloxamer 188 has been used (37) to study the development of tumor metastasis in rats. Treatment of rats, which had been intravenously administered tumor cells, with the poloxamer decreased the incidence of pulmonary metastasis

from 85.3% in the control to only 16.1%. The poloxamer property believed responsible for this application is its ability to prevent microvascular sludging of red cells, as well as its lack of toxicity. This is but one of a few hundred articles in various medical and pharmaceutical journals which describe the use of a poloxamer being studied in a research project.

In the paper industry, the preparation of a single transfer coating for paper utilized a poloxamer on a production scale (38). Poloxamer 182 was used as the wetting and dispersing agent to apply a coating on a backing surface of the paper sheet. After drying, the coating is tested for transfer properties by typing the front surface of the sheet with a second untreated sheet in facial contact with the coating. The second sheet was found to apply a transferred copy which had a sharp blue image and offered good smudge resistance.

It has been reported (39) that the moisture level in a sheet of cellulose, such as paper, can be stabilized by using a polyalkylene oxide as a stabilizing agent and a poloxamer to enhance the rate of absorption of the polyglycol by the sheet material. Using polyoxyethylene glycols of molecular weights varying from 400 to 4000, a dramatic decrease occurred in the time needed to saturate the sheet, from more than 2 min to less than 5 sec, upon addition of the block polymer. The wetting properties of the poloxamers proved useful in this application.

The textile industry has recognized the antistatic properties of the poloxamines and their derivatives. This is due to the following: (a) the presence of the two pairs of unshared electrons on the tertiary nitrogen atoms provides a slight cationic effect; (b) the poloxamine branched structure more readily lends itself to crosslinking and increased viscosity, and (c) the superior poloxamine thermal stability is believed to be due to the ability to form amine oxides upon oxidation. Hydrophobic fibers having antistatic properties were made (40) by incorporating an ester of a dibasic acid with a poloxamine having up to 30% propylene oxide at a mol wt of 200-10000 into the spin bath prior to spinning the nylon fiber.

A poloxamine having a mol wt between 4000-135,000 has been reported (41) to give excellent antistatic action in nylon 6 when used at 1-12%, based on the weight of the nylon. The fibers showed excellent antistatic activity through 25 washes.

An effective antistatic agent giving improved performance to nylon was obtained (42) by chain extending a poloxamine with a diepoxide or a diisocyanate. Even better antistatic effectiveness was reported achieved by further reaction with a sulfuric acid derivatives, such as sodium paratoluene sulfonate. This increased the viscosity of the polymer, thus making it more compatible with the high viscosity nylon melt prior to spinning.

A novel method for softening laundry was reported (43) by tumbling it in a damp state with coated polystyrene foam spheres. By dip-coating the spheres in a blend of a poloxamer 407, sodium tallow alcohol sulphate slurry, and ethyl alcohol, the softener was readily transferred to the laundry while tumbling in a dryer.

Improved lubricating oil compositions containing lubricating viscosity and conventional gear oil and hydraulic oil additives may be obtained (44) by incorporating relatively small amounts, as little as 0.01%, of a poloxamine with a molecular weight range of 1650-15000 and an ethylene oxide content of about 10-50%. The poloxamine addition serves to improve the oil compositions by giving improved rust protection, by a standardized test, by improving rate of demulsibility in a standard demulsification test, and by giving less emulsion sludge in a standard engine test. The surfactant properties reponsible for this improvement include its wetting, interfacial tension lowering, and dispersing abilities.

REFERENCES

1. CTFA Cosmetic Ingredient Dictionary, 1st Ed., Bull. No. 9, CTFA Inc., Washington, DC (March 1975).
2. Vaughn, T.H., H.R. Suter, L.G. Lundsted, and M.G. Kramer, JAOCS 28:294 (1951).
3. Jackson, D.R., and L.G. Lundsted, U.S. Pat. 3,036,118 (1962).
4. Lundsted, L.G., U.S. Pat. 2,979, 528 (1961).
5. Rudner, B., and A.G. Prapas, U.S. Pat. 3,189,653 (1965).
6. Patton, J.T. Jr., U.S. Pat. 3,101,374 (1963).
7. "The Wonderful World of Pluronic Polyols," BASF Wyandotte Corp., Wyandotte, MI (1971).
8. "Pluronic R Nonionic Surface Active Agents," 0-110, BASF Wyandotte Corp., Wyandotte, MI (1971).
9. "Tetronic Series Nonionic Surfactants," 0-85R, BASF Wyandotte Corp., Wyandotte, MI (1970).
10. "Pluradot Polyols," 0-86R, BASF Wyandotte Corp., Wyandotte, MI (1971).
11. Pluronic Polyols Toxicity and Irritation Data, 3rd Ed., Revised, BASF Wyandotte Corp., Wyandotte, MI (1971).
12. Gleason, M.N., R.E. Gosselin, and H.C. Hodge, "Clinical Toxicology of Commercial Products," 2nd Ed., Williams & Wilkins Co., Baltimore, MD (1963).
13. Mankowich, A.M., J. Phys. Chem. 58:1028 (1954).
14. Bell, W.E., Ibid. 63:299 (1959).
15. Dwiggins, C.W. Jr., R.J. Bolen, and H.N. Dunning, Ibid. 64:1175 (1960).
16. Becher, P., Ibid. 63:1615 (1959).
17. Ross, S., and J.P. Olivier, Ibid. 63:1671 (1959).
18. Schmolka, I.R., and A.J. Raymond, JAOCS 42:1088 (1965).
19. Saski, W., and S.G. Shah, J. Pharm. Sci. 54:71 (1965).
20. Sheth, P.B., Diss. Abstr. 28:974 (1967).
21. Anderson, R.A., Pharm. Acta Helv. 47(5):304 (1972).
22. Jacobs, J., R.A. Anderson, and T.R. Watson, J. Pharm. Pharmacol. 24:586 (1972).
23. Cowie, J.M.G., and A.F. Sirianni, JAOCS 43:572 (1966).
24. Willix, R.L.S., J. Pharm. Sci. 59:1439 (1970).
25. McDonald, C., and C.K. Wong, J. Pharm. Pharmacol. 26:556 (1974).
26. Zinner, D.D., L.F. Duany, and H.J. Lutz, IADR Abstract L340, London (1975).
27. Januszewski, J.P., U.S. Pat. 3,639,563 (1972).
28. Unilever NV, Neth. Pat. 7,103,689 (1971).
29. Curry, K.B., and A.I. Sahir, Ger. Pat. 2,140,321 (1972).
30. Garcia, L.A., U.S. Pat. 3,880,989 (1975).
31. Green, J., K.H. Baggaley and B. Morgan, U.S. Pat. 3,916,008 (1975).
32. Arambulo, A.S., M.S. Lie, A.L. Rosen, G. Dobben, and D.M. Long, Drug Dev. Commun. 1:73 (1974).
33. Geyer, R.P., Fed. Proc. 34:1499 (1975).
34. Barnes, M., M.R. Billany, and A.J. Sandoe, Mfg. Chem. and Aerosol News 44(10):29 (1973).
35. Miskel, J.J., and F.S. Hom, U.S. Pat. 3,867,521 (1975).
36. Meyer, R.M., and E.E. Bartley, U.S. Pat. 3,686,416 (1972).
37. Silk, M., and E. Sigman, Cancer 29(1):171 (1972).
38. Rizner, J.S., U.S. Pat. 3,446,647 (1969).
39. Wennergren, J.J., and L.G. Samuelson, U.S. Pat. 3,674,632 (1972).
40. Lofquist, R.A., and B.T. Hayes, U.S. Pat. 3,655,821 (1972).
41. Weedon, G.C., and L. Crescentini, U.S. Pat. 3,755,497 (1973).
42. Crescentini, L., and R.L. Wells, U.S. Pat. 3,287,524 (1974).
43. Hewitt, G.T., and A.S. Giordano, U.S. Pat. 3,676,199 (1972).
44. Papay, A.G., B.W. Matthews, and A.S. Thomas, U.S. Pat. 3,928,219 (1975).

[Received August 18, 1976]

This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☑ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☑ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☑ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.
As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.